Application for the extension of authorization of DHA and EPA-rich Algal Oil from *Schizochytrium* sp.

Submitted pursuant to
Regulation (EC) No 258/97 of the European Parliament and of the Council of 27th January 1997 concerning novel foods and novel food ingredients

Prepared by: DSM Nutritional Products
6480 Dobbin Road
Columbia, MD 21045
USA

28 September 2012

Application for the extension of authorization of DHA and EPA-rich Algal Oil from *Schizochytrium* sp.

Table of Contents

Page

List of Tables

Application for the extension of authorization of DHA and EPA-rich Algal Oil from *Schizochytrium* sp.

EXECUTIVE SUMMARY AND CONCLUSIONS

DSM Nutritional Products (DSM, formerly Martek Biosciences Corporation) has recently gained approval for docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)-rich oil produced from *Schizochytrium* sp. (hereinafter "DHA and EPA-rich oil"), for use as a nutritional ingredient in a range of foodstuffs at specified maximum levels of inclusion. These foodstuffs include food supplements at a maximum DHA and/or EPA content of "250 mg per daily dose as recommended by the manufacturer for normal population; 450 mg per daily dose as recommended by the manufacturer for pregnant and lactating women (Food Standards Agency - ACNFP, 2012a,b). Recently the European Food Safety Authority (EFSA) has issued 2 scientific opinions related to DHA and EPA and health claims related to triglyceride maintenance and blood pressure maintenance that recommend daily doses of between 2 and 3 g (EFSA, 2011a,b)

In support of such levels on 27th July 2012 EFSA published its *Scientific Opinion on the Tolerable Upper Intake Level of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA).* (EFSA, 2012), which concluded as follows:

"The Panel considers that supplemental intakes of EPA and DHA combined at doses up to 5 g/day …do not raise safety concerns for the adult population."

Consequently, in anticipation of triglyceride and blood pressure claims being now adopted into the Register, DSM wishes to extend the use of DHA and EPA-rich Oil to up to a maximum DHA and EPA content of "3000 mg per daily dose as recommended by the manufacturer for normal population; 450 mg per daily dose as recommended by the manufacturer for pregnant and lactating women". Such higher intakes can be achieved by taking DHA and EPA-rich oil in a variety of dosed forms including capsules and liquids, however, of course taking such doses will obviously only be desirable to target individuals for those claims.

DSM Nutritional Products is hereby presenting its application for the extension of the authorisation of DHA and EPA-rich algal oil from *Schizochytrium* sp. as a novel food ingredient under *Regulation (EC) No 258/97 of the European Parliament and of the Council of 27th January 1997 concerning novel foods and novel food ingredients* (European Parliament and Council of the European Union, 1997). Under Article 1, point 2, DHA and EPA-rich oil has already been classified under group:

"(d) foods and food ingredients consisting of or isolated from micro-organisms, fungi or algae".

In this extension application the content of the original application still applies in relation to the Scientific Guidance for dossiers (Commission of the European Communities, 1997) and Sections:

I Specification of the Novel Food
II. Effect of the Production Process Applied to the Novel Food
III. History of Source Organism
XII. Microbiological Information

Based on both the data originally presented specifically on DHA and EPA-rich oil and on the recent review of EFSA concluding that up to 5g of DHA and EPA per day can be safely consumed by the general population, and considering the specific risk management and labelling provisions laid down under Commission Directive 2002/46 on food supplements, we conclude that such an extension of use should not raise safety concerns (European Parliament and the Council of the European Union, 2002).

Application for the extension of authorization of DHA and EPA-rich Algal Oil from *Schizochytrium* sp.

INTRODUCTION

DSM Nutritional Products (DSM, formerly Martek Biosciences Corporation) has recently gained approval for docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)-rich oil produced from *Schizochytrium* sp. (hereinafter "DHA and EPA-rich oil"), for use as a nutritional ingredient in a range of foodstuffs at specified maximum levels of inclusion (ACNFP, 2012a,b). These foodstuffs include food supplements at a maximum DHA and/or EPA content of "250 mg per daily dose as recommended by the manufacturer for normal population; 450 mg per daily dose as recommended by the manufacturer for pregnant and lactating women". Recently the European Food Safety Authority (EFSA) has issued 2 scientific opinions related to DHA and EPA and health claims related to triglyceride maintenance and blood pressure maintenance that recommend daily doses of between 2 and 3 g.

In support of such levels on 27th July 2012 EFSA published its *Scientific Opinion on the Tolerable Upper Intake Level of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA)* (EFSA, 2012), which concluded as follows:

"The Panel considers that supplemental intakes of EPA and DHA combined at doses up to 5 g/day …do not raise safety concerns for the adult population."

Consequently, in anticipation of triglyceride and blood pressure claims being now adopted into the Register, DSM wishes to extend the use of DHA and EPA-rich Oil to up to a maximum DHA and EPA content of "3000 mg per daily dose as recommended by the manufacturer for normal population; 450 mg per daily dose as recommended by the manufacturer for pregnant and lactating women".

DSM is hereby presenting its application for the extension of the authorisation of DHA and EPA-rich algal oil from *Schizochytrium* sp. as a novel food ingredient under *Regulation (EC) No 258/97 of the European Parliament and of the Council of 27th January 1997 concerning novel foods and novel food ingredients* (European Parliament and Council of the European Union, 1997). Under Article 1, point 2, DHA and EPA-rich oil has already been classified under group:

"(d) foods and food ingredients consisting of or isolated from micro-organisms, fungi or algae".

This application has been prepared in accordance with the EU recommendation of 29 July 1997, where relevant (Commission of the European Communities, 1997). Under these guidelines DHA and EPA-rich oil would fall under class: 2.2 ('complex novel food from a non-

GM source', 'the source of the novel food has no history of use in the community'). Consistent with the recommendations, Sections IV to VIII of the EU recommendation are not applicable to DHA-rich algal oil since no GM technology is involved.

1. ADMINISTRATIVE DATA

The present petition is submitted by DSM Nutritional Products (DSM), manufacturer of DHA and EPA-rich oil from *Schizochytrium* sp. (DHA and EPA-rich oil).

Address of the applicant is as follows:

DSM Nutritional Products
6480 Dobbin Road
Columbia, MD 21045
USA

2. GENERAL DESCRIPTION

DHA and EPA-rich oil is classified as Class 2.2, *i.e.*, “complex Novel Food from non-GM Source”; the source of the NF has no history of use in the Community.

3. IDENTIFICATION OF THE ESSENTIAL INFORMATION REQUIREMENTS

In accordance with the EU guidelines, the requirements for the submission of a dossier for this class of Novel Food are as follows:

I. Specification of the Novel Food
II. Effect of the Production Process Applied to the Novel Food
III. History of Source Organism
IX. Anticipated Intake/Extent of Use
X Information from Previous Human Exposure to the Novel Foods or its Source
XI. Nutritional Information
XII. Microbiological Information
XIII. Toxicological Information

However, since this application refers only to an extension of use, we do not include any new information under Sections I, II, III, or XII.

I SPECIFICATION OF THE NOVEL FOOD

According to the Scientific Committee on Food (SCF) guidelines as published in the EU recommendation of 29 July 1997 (Commission of the European Communities, 1997), the following questions must be asked at this stage:

1. "Is there an appropriate specification (including species, taxonomy *etc*. for living organisms) to ensure that the Novel Food marketed is the same as that evaluated?"

2. "Is the information representative of the Novel Food when produced on a commercial scale?"

3. "Is appropriate analytical information available on the potential toxic inherent constituents, external contaminants and nutrients?"

These questions have all been answered in our previous submission and the ACNFP Opinion (ACNFP, 2012a,b) which concluded:

"The Committee was satisfied that the composition of DHA-O did not give rise to any safety concerns."

The approval specification is laid down in the Food Standard Agency's letter dated 6th July 2012 as defined in Table 1 below (ACNFP, 2012a,b). In its approval letter, the FSA also noted that in response to member states comments at the "60 day" state:

Table 1 Specification of DHA (Docosahexaenoic Acid) and EPA (Eicosapentaenoic Acid)–rich Oil from Microalgae *Schizochytrium* sp.

Test	Specification
Acid value	Not more than 0,5 mg KOH/g
Peroxide value (PV)	Not more than 5,0 meq/kg oil
Moisture and volatiles	Not more than 0,05%
Unsaponifiables	Not more than 4,5%
Trans-fatty acids	Not more than 1%
DHA content	Not less than 22,5%
EPA content	Not less than 10%

Note: All food products containing DHA and EPA-rich oil from *Schizochytrium* sp. should demonstrate oxidative stability by appropriate and recognised national/international test methodology (e.g. AOAC).

The specification for DHA and EPA-rich oil has not changed.

II EFFECT OF THE PRODUCTION PROCESS APPLIED TO THE NOVEL FOOD

Based on Commission Recommendation 97/618/EC decision trees the following questions must be addressed pertaining to the intake/extent of use of the novel food (Commission of the European Communities, 1997):

1. “Does the Novel Food undergo a production process?”
2. “Is there a history of use of the production process for the food?”
3. “Does the process result in a significant change in the composition or structure of the Novel Food compared to its traditional counterpart?”
4. “Is information available to enable identification of the possible toxicological, nutritional and microbiological hazards arising from the use of the process?”
5. “Are the means identified for controlling the process to ensure that the Novel Food complies with its specification?”
6. “Has the process the potential to alter the levels of Substances with an adverse effect on public health, in the Novel Food?”
7. “After processing is the Novel Food likely to contain micro-organisms of adverse public health significance?”

These questions were answered within our previous application dossier and in the ACNFP’s published opinion (ACNFP, 2012a,b). This opinion concluded:

“*The Committee noted that the production process was similar to that used for the production of DHA-S and, although the differences in the extraction procedure were noted, Members were content that they did not give cause for concern.*”

In its approval letter in response to member states comments (ACNFP, 2012a,b) the FSA also noted:

“(c) You indicated that the antioxidants which are added to this oil are approved under regulation (EC) 1333/2008 and that, typically, these are ascorbyl palmitate and tocopherols (European Parliament and the Council of the European Union, 2008). You also noted that all your omega-3 rich algal oils are packaged under nitrogen and in opaque packaging with low oxygen permeability.”

III HISTORY OF SOURCE ORGANISM

Based on Commission Recommendation 97/618/EC decision trees the following questions must be addressed pertaining to the history of the source organism (Commission of the European Communities, 1997):

1. “Is the novel food obtained from a biological source, *i.e*., a plant, animal or microorganism?”

2. “Has the organism used as the source of the novel food been derived using GM?”

3. “Is the source organism characterized?”

4. “Is there information to show that the source organism and/or foods obtained from it are not detrimental to human health?”

These questions were answered within our previous application dossier and in the ACNFP’s published opinion (ACNFP, 2012a,b). This opinion concluded:

“The Committee accepted that Schizochytrium sp had previously been used to produce DHA rich oils and although DHA-O was produced from a newly characterised member of the genus, as there were no reports of toxins being produced by any members of the Class which includes the genus Schizochytrium, the use of the organism as a source of the oil did not give cause for concern. The Committee also accepted that the test results confirming the absence of domoic acid and prymnesin offered additional reassurance in this regard.”

SECTIONS IV TO VIII

Sections IV to VIII of the EU recommendation are not applicable to DHA and EPA-rich algal oil since no GM technology is involved.

IX ANTICIPATED INTAKE/EXTENT OF USE

Based on Commission Recommendation 97/618/EC decision trees the following questions must be addressed pertaining to the intake/extent of use of the novel food (Commission of the European Communities, 1997):

1. "Is there information on the anticipated uses of the novel food based on its properties?"

2. "Is there information to show anticipated intakes for groups predicted to be at risk?"

3. "Will introduction of the novel food be restricted geographically?"

4. "Will the novel food replace other foods in the diet?"

We will address each point in turn in this section.

IX.1 Is there information on the anticipated uses of the novel food based on its properties?

Proposed Uses

In this application we wish only to extend the uses currently approved for DHA and EPA-rich oil for supplements. The current approval (ACNFP, 2012a,b) states:

Food Category	**Maximum Use-Level of DHA + EPA (mg/100 g) unless otherwise stated**
Food Supplements	250 mg per daily dose as recommended by the manufacturer for normal population; 450 mg per daily dose as recommended by the manufacturer for pregnant and lactating women

We simply wish to amend as follows:

Food Category	**Maximum Use-Level of DHA + EPA (mg/100 g) unless otherwise stated**
Food Supplements	3000 mg per daily dose as recommended by the manufacturer for normal population; 450 mg per daily dose as recommended by the manufacturer for pregnant and lactating women

Food supplement products may be presented in various dosed forms including capsules or liquid form depending on desired dose. For example, based on a typical combined DHA and EPA content of 50% (see Table 4 of original application, ACNFP, 2011) this might range from one 500 mg soft gel delivering 250 mg per day for the general population to either 6 x 1g capsules (2 capsules at meal times) or 6 g of liquid oil (usually flavoured like cod liver oil has been traditionally) for people wishing to maintain their triglyceride and/or blood pressure

levels, as part of a healthy diet.The reasoning for this amendment is discussed in more detail in Section XI below.

IX.2 Is there information to show anticipated intakes for groups predicted to be at risk?

In its original opinion (ACNFP, 2012a,b) the FSA concluded:

"*The Committee was content that the minor changes to the use levels would not lead to an increase in the level of consumption amongst the general population. Members noted the high-dose supplements which are targeted at pregnant and nursing mothers were also in line with a recent health claim request that had recently been evaluated by EFSA and noted that this may lead to an increase in gestation periods*"

In its approval letter the FSA also stated:

"The ACNFP also recommended that this be taken into account when monitoring possible adverse events following the widespread introduction of this novel oil into the diet."

As an extra precaution we propose not to amend the maximum levels intended for pregnant and lactating women, and to keep them in line with the current recommendations (Advisory Intake) of EFSA as discussed in the original submission and opinion.

DSM has written regulatory, medical, and clinical standard operating procedures (SOPs) for obtaining, evaluating and reporting adverse experiences (AEs) and serious adverse experiences (SAEs) occurring in clinical trials and in reports from marketed use of its products. DSM monitors product AEs during sponsored clinical studies or during investigator-initiated studies for which product is supplied. Also monitored are AEs reported to DSM through an established toll free (800) phone number and Web Site.

IX.3 Will introduction of the novel food be restricted geographically?

There are no proposed geographical restrictions. DHA and EPA-rich oil is an environmentally sustainable vegetarian alternative to fish oil. This should be a highly desirable prospect for all Member States at a time of stretched fishing stocks and the increasing amount of evidence supporting the importance of DHA and EPA to their citizens' health.

IX.4 Will the novel food replace other foods in the diet?

As stated earlier, DHA and EPA-rich oil is a simple replacement for fish and other algal oils in the European diet. It is proposed at "like-for like" uses and levels of addition, with the same nutritional value. Currently fish oils have no restrictions over their maximum use level in food supplement products, or any others. The recent EFSA Opinion on the safety of DHA and EPA (EFSA, 2012) summarised EU and other European intakes as follows:

"Mean daily intakes of EPA and DHA from food only were between 127 mg/day (Germany, women, 18-24 years) and 295 mg/day (Germany, men, 45-54 years). Daily intakes of EPA

and DHA in the highest percentiles of consumption (P95) were between 285 mg/day (The Netherlands, women, 19-30 years) and 1,115 mg/day (Belgium, women, 18-39 years), going up to 1278 mg/day (Ireland, 51-64 years) when food and food supplements were considered together. Mean intakes of EPA and DHA in high fish consumers from food only were up to 2700 mg/day (France, 18 years, fifth quintile of EPA-DHA intake). No surveys reported on EPA and DHA intakes from food and supplements combined in high seafood consumers.

Mean daily intakes of EPA, DHA and DPA were about 400 to 500 mg/day (France, women 35 years and males 45 years), increasing to 2,570 mg/day (Norway*, males, 16-79 years, fourth quartile of n-3 LCPUFA) when food and food supplements were considered together. Data from another survey considering food and fish oil combined for total n-3 LCPUFA were within these ranges."

*Note Norway is not an EU member state and its intakes are disproportionately higher than for most EU member states

Food supplement use is controlled under the conditions laid down for labelling and presentation under food supplements legislation would prevent involuntary excessive dosing. Specifically these conditions are laid down in Article 6, point 3 of *Directive 2002/46/EC on food supplements* (European Parliament and the Council of the European Union, 2002), as follows:

3. Without prejudice to Directive 3000/13/EC, the labelling shall bear the following particulars (European Parliament and Council of the European Union, 2000):

(a) the names of the categories of nutrients or substances that characterise the product or an indication of the nature of those nutrients or substances;

(b) the portion of the product recommended for daily consumption;

(c) a warning not to exceed the stated recommended daily dose;

(d) a statement to the effect that food supplements should not be used as a substitute for a varied diet;

(e) a statement to the effect that the products should be stored out of the reach of young children.

Therefore there are appropriate specific risk management measures to prevent the over consumption of food supplements. Food supplement products may be presented in various dosed forms including capsules or liquid form depending on desired dose. For example, based on a typical combined DHA and EPA content of 50% (see Table 4 of original application, ACNFP, 2011) this might range from one 500 mg soft gel delivering 250 mg per day for the general population to either 6 x 1g capsules (2 capsules at meal times) or 6 g of liquid oil (usually flavoured like cod liver oil has been traditionally) for people wishing to maintain their triglyceride and/or blood pressure levels, as part of a healthy diet.

X INFORMATION FROM PREVIOUS HUMAN EXPOSURE TO THE NF OR ITS SOURCE

Based on Commission Recommendation 97/618/EC decision trees the following questions must be addressed pertaining to the history of the source organism (Commission of the European Communities, 1997):

1. “Is there information from previous direct, indirect, intended, or unintended human exposure to the novel food or its source which is relevant to the EU situation with respect to production, preparation, population, lifestyles and intakes?”

2. “Is there information to demonstrate that exposure to the novel food is unlikely to give rise to mitochondrial, toxicological and/or allergenicity problems?”

These points are addressed in the section that follows.

X.1 Is there information from previous direct, indirect, intended, or unintended human exposure to the novel food or its source which is relevant to the EU situation with respect to production, preparation, population, lifestyles and intakes?

The current approvals for DHA and EPA-rich microalgal oil are laid down in Table 2 below. We seek only to extend the use in food supplements. The remaining food uses are self-limiting, that is to say it would in most cases not be possible technologically (stability, taste, *etc*.) or economically to put 3000 mg into a daily serving.

Table 2 Uses of DHA (Docosahexaenoic Acid) and EPA (Eicosapentaenoic Acid)-rich Oil from Microalgae *Schizochytrium* sp.

Food Category	**Maximum Use-Level of DHA + EPA (mg/100 g) unless otherwise stated**
Food Supplements	250 mg per daily dose as recommended by the manufacturer for normal population; 450 mg per daily dose as recommended by the manufacturer for pregnant and lactating women
Dietary foods for special medical purposes	In accordance with the particular nutritional requirements of the persons for whom the products are intended
Foods intended for use in energy-restricted diets for weight reduction	250 mg per meal replacement
Other foods for particular nutritional uses (PARNUTS), as defined in Directive 2009/39/EC (European Parliament and the Council of the European Union, 2009) excluding infant and follow on formula	200 mg/100 g
Bakery Products, Breads and Rolls, Sweet Biscuits	200 mg/100 g
Breakfast Cereals	500 mg/100 g
Cooking Fats	360 mg/100 g
Dairy Analogues (except drinks)	600 mg/100 g for cheese; 200 mg/100 g for soy and imitation milk products (excluding drinks)
Dairy Products (except milk-based drinks)	600 mg/100 g for cheese; 200 mg/100 g for milk products (including milk, fromage frais and yoghurt products; excluding drinks)
Non-alcoholic Beverages (including dairy analogue and milk-based drinks)	80 mg/100 g
Cereal/Nutrition Bars	500 mg/100 g
Spreadable Fats and Dressings	600 mg/100 g

X.2 “Is there information to demonstrate that exposure to the novel food is unlikely to give rise to mitochondrial, toxicological and/or allergenicity problems?”

The toxicological and allergenicity aspects of DHA and EPA-rich Oil were discussed in the previous submission and opinion from the ACNFP (ACNFP, 2011, 2012a,b). This is also discussed in Section XIII below.

XI NUTRITIONAL INFORMATION ON THE NOVEL FOOD

1. "Is there information to show that the novel food is nutritionally equivalent to existing foods that it might replace in the diet?"

We will address this point within this section.

XI.1 Is there information to show that the novel food is nutritionally equivalent to existing foods that it might replace in the diet?

This issue has been extensively addressed in the original application dossier and the ACNFP Opinion, which concluded:

"The Committee accepted that the nutritional information provided was appropriate and the non-fat nutritional profile of a product containing the novel ingredient would not be significantly different when compared with an equivalent product fortified with fish oil. The Committee also noted that the fatty acid profile of the product was broadly comparable with existing fish oil derived products and, as such, would be unlikely to give rise to safety concerns. The Committee also noted that the applicant does not discuss the nutritional profile of the product in terms of its composition as a fat but, as it is almost entirely composed of triglycerides, a caloric value of 9 kcal will therefore be used on nutritional labels, as is currently used for DHA-S" (DHA-rich oil from *Schizochytrium* sp.).

Recently EFSA has issued 2 scientific opinions related to DHA and EPA and health claims which form the basis of why DSM is applying to extend the maximum use levels of DHA and EPA-rich oil in supplements:

1. **DHA and EPA and Maintenance of normal (fasting) blood concentrations of triglycerides**
   "On the basis of the data presented, the Panel concludes that a cause and effect relationship has been established between the consumption of DHA and the maintenance of normal (fasting) blood concentrations of triglycerides. In order to obtain the claimed effect, 2 g per day of DHA should be consumed in one or more servings. The target population is adult men and women." (EFSA, 2010a)

2. **DHA and EPA and Maintenance of Normal Blood Pressure**
   "The claimed effect is "helps maintain normal blood pressure". The target population is assumed to be the general population. Maintenance of normal blood pressure is beneficial to human health. A cause and effect relationship has been established between the dietary intake of EPA and DHA and the reduction of blood pressure. The following wording reflects the scientific evidence: "DHA and EPA contribute to the maintenance of normal blood pressure".
   Intakes of EPA and DHA of about 3 g/d are required to obtain the claimed effect.

   DHA and EPA and Maintenance of normal (fasting) blood concentrations of

triglycerides

The target population is adult men and women. The claimed effect is “healthy triglyceride levels”. The target population is assumed to be the general population. Maintenance of normal blood triglyceride levels is beneficial to human health. A cause and effect relationship has been established between the consumption of EPA and DHA and the reduction of (fasting) blood concentrations of triglycerides. EPA, DHA and DPA related health claims. The following wording reflects the scientific evidence: “DHA and EPA contribute to the maintenance of normal concentrations of triglycerides”.

Intakes of EPA and DHA of 2-4 g/d are required to obtain the claimed effect. The target population is adult men and women.” (EFSA, 2010b).

Thus the use of such levels of DHA and EPA will be beneficial to individuals wishing to specific target individuals, as part of a balanced diet.

However, the higher levels of DHA, EPA and DPAn-3 required to carry these claims raised concerns with at least one member state which resulted in EFSA being asked for an overall opinion on the upper safe level of these ingredients, *per se*, prior to inclusion of these claims onto the European Union Register of Approved health Claims. On 27th July 2012 EFSA published its positive opinion, which is discussed in Section XIII below.

XII MICROBIOLOGICAL INFORMATION

Based on Commission Recommendation 97/618/EC decision trees the following questions must be addressed pertaining to microbiological information available for the novel food (Commission of the European Communities, 1997):

1. “Is the presence of any microorganisms or their metabolites due to the novelty of the product/process?”

This question was addressed in the original application and ACNFP Opinion (ACNFP, 2012a,b) which concluded:

“The Committee accepted the data provided in the application although Members regarded the possibility of contamination by cyanobacteria to be one that should not be discounted. In regard to this point, Members were reassured by the quality control regime and confirmation from the applicant that that the fermentation proceeds in the absence of light under axenic conditions. The Committee accepted that these measures were sufficient to ensure that any risk of Cyanobacterial contamination was no greater than for any other closed system fermentation process used in food production.”

XIII ADDITIONAL TOXICOLOGICAL AND HUMAN SAFETY INFORMATION

Based on Commission Recommendation 97/618/EC decision trees the following questions must be addressed pertaining to toxicological information available on the novel food (Commission of the European Communities, 1997):

1. “Is there a traditional counterpart to the novel food that can be used as a baseline to facilitate the toxicological assessment?”

2. “Compared to the traditional counterpart, does the novel food contain any new toxicants or changed levels of existing toxicants?”

OR

3. “Is there information from a range of toxicological studies appropriate to the novel food to show that the novel food is safe under anticipated conditions of preparation and use?”

4. “Is there information which suggests that the novel food might pose an allergenic risk to humans?”

All of these aspects were reviewed in the original dossier and opinion from the ACNFP (ACNFP, 2011, 2012a,b).

XIII.1 Is there a traditional counterpart to the novel food that can be used as a baseline to facilitate the toxicological assessment?

In the original dossier comparisons were made to both fish oils and other algal oils. The ACNFP opinion noted:

“In addition to the toxicological studies carried out on DHA and EPA-rich oil (see below), the applicant notes that its traditional counterpart, fish oil, is widely used both in food supplements and in fortified foods in the EU without restriction.”

XIII.2 Compared to the traditional counterpart, does the novel food contain any new toxicants or changed levels of existing toxicants?

In the original dossier clearly demonstrated that there are no added toxicants and that the nature of manufacture of DHA and EPA-rich oil in closed vessels with tight production and environmental controls mean that the risk of contamination from environmental sources is much lower than that for fish and fish oil.

XIII.3 Is there information from a range of toxicological studies appropriate to the novel food to show that the novel food is safe under anticipated conditions of preparation and use?

The toxicity studies presented on DHA and EPA-rich oil were reviewed in the original opinion (ACNFP, 2012a,b). They included 14-day and 90-day rat and genotoxicity studies.

Under the conditions of the pivotal 90-day rat study and based on the toxicological endpoints evaluated, the no-observed-adverse-effect level (NOAEL) for DHA and EPA-rich oil in the diet was judged to be 5% (50,000 mg/kg) for male and female rats, equivalent to 3149 and 3343 mg/kg body weight/day, for male and female rats respectively.

Based on our proposed maximum dose of a 3000 mg food supplement and a 60 kg adult this is approximately 60 mg/kg body weight/day. This therefore provides an approximate 65-fold safety factor compared the above NOAEL.

Furthermore, based on the comparison of DHA and EPA from all sources EFSA have recently concluded that the available data are not sufficient to establish a tolerable upper intake level for n-3 LCPUFA (DHA, EPA, and DPA, individually or combined) for any population group and that supplemental intakes of EPA and DHA combined at doses up to 5 g/day do not raise safety concerns for the adult population.

XIII.4 Is there information which suggests that the novel food might pose an allergenic risk to humans?

This was discussed in the original dossier and ACNFP opinion as follows:

“The level of residual protein in DHA-O is less than 0.02%, measured by the Kjeldahl method. The applicant notes that DHA-S is produced from very similar source materials and also contains low levels of protein (<0.1%), and has not been associated with any serious adverse events. The applicant also notes that reports of respiratory and dermatologic responses (including allergy) to microalgae have been restricted to human exposure to bluegreen algae.”

CONCLUSIONS

DSM wish to increase the maximum permitted level of DHA plus EPA from DHA and EPA-rich oil in food supplements for the normal population excluding pregnant and lactating women to 3 g per day to permit the use of proposed health claims relating to the maintenance of healthy triglycerides and blood pressure. Such higher intakes can be achieved by target individuals taking DHA and EPA-rich oil in a variety of dosed forms including capsules and liquids. Based on both the data originally presented specifically on DHA and EPA-rich oil and on the recent review of EFSA concluding that up to 5g of DHA and EPA per day can be safely consumed by the general population, and considering the specific risk management and labelling provisions laid down under Commission Directive 2002/46 on food supplements, we conclude that such an extension of use should not raise safety concerns (European Parliament and the Council of the European Union, 2002).

REFERENCES

ACNFP. *DHA and EPA-rich Algal Oil: Application from Martek Biosciences Corporation, for the authorisation of DHA and EPA-rich algal oil (DHA-O) under the Novel Food Regulation (EC) 258/97*. Food Standards Agency (FSA), Advisory Committee on Novel Foods and Processes (ACNFP), London, Engl.; 2011. Available from: http://acnfp.food.gov.uk/assess/fullapplics/dhanadeparichalgaloil/.

ACNFP. *DHA and EPA Rich Oil from the Microalgae Schizochytrium*. (NFU 786). Food Standards Agency (FSA), Advisory Committee on Novel Foods and Processes (ACNFP), London, Engl.; 2012a. Available from: http://ec.europa.eu/food/food/biotechnology/novelfood/dha_o_authorisation_letter_06072012_en.pdf [July 6, 2012].

ACNFP. *Initial Opinion: A DHA and EPA Rich Oil from the Microalgae Schizochytrium*. (NFU 786). Food Standards Agency (FSA), Advisory Committee on Novel Foods and Processes (ACNFP), London, Engl.; 2012b. Available from: http://www.food.gov.uk/multimedia/pdfs/inopdhamartek.pdf [Dec. 9, 2012].

Commission of the European Communities. Commission Recommendation of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients and the preparation of initial assessment reports under Regulation (EC) No 258/97 of the European Parliament and of the Council (97/618/EC) [L253]. *Official Journal of the European Communities* 1997, 40: 1-36. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31997H0618:EN:HTML.

EFSA. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion the substantiation of a health claim related to docosahexaenoic acid (DHA) and maintenance of normal (fasting) blood concentrations of triglycerides (ID 533, 691, 3150), protection of blood lipids from oxidative damage (ID 630), contribution to the maintenance or achievement of a normal body weight (ID 629), brain, eye and nerve development (ID 627, 689, 704, 742, 3148, 3151), maintenance of normal brain function (ID 565, 626, 631, 689, 690, 704, 742, 3148, 3151), maintenance of normal vision (ID 627, 632, 743, 3149) and maintenance of normal spermatozoa motility (ID 628) pursuant to Article 13(3) of Regulation (EC) no 1924/2006. (Question no EFSA-Q-2008-1320, EFSA-Q-2008-1416, EFSA-Q-2008-1417, EFSA-Q-2008-1478, … (*etc.*), adopted on 9 July 2010 by European Food Safety Authority). *EFSA Journal* 2010a, 8: 1734. (27 pp.). doi:10.2903/j.efsa.2010.1734. Available from: http://www.efsa.europa.eu/en/efsajournal/pub/1734.htm.

EFSA. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of health claims related to eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), docosapentaenoic acid (DPA) and maintenance of normal cardiac function (ID 504, 506, 516, 527, 538, 703, 1128, 1317, 1324, 1325), maintenance of normal blood glucose concentrations (ID 566), maintenance of normal blood pressure (ID 506, 516, 703, 1317, 1324), maintenance of normal blood HDL-cholesterol concentrations (ID 506), maintenance of normal (fasting) blood concentrations of triglycerides (ID 506, 527, 538, 1317, 1324, 1325), maintenance of normal blood LDL-cholesterol concentrations (ID 527, 538, 1317, 1325, 4689), protection of the skin from photo-oxidative (UV-induced) damage (ID 530), improved absorption of EPA and DHA (ID 522, 523), contribution to the normal function of the immune system by decreasing the levels of eicosanoids, arachidonic acid-derived mediators and pro-inflammatory cytokines (ID 520, 2914), and “immunomodulating agent” (4690) pursuant to Article 13(1) of Regulation (EC) no 1924/2006. (Question no EFSA-Q-2008-1291, EFSA-Q-2008-1293, EFSA-Q-2008-1303, EFSA-Q-2008-1309, … (*etc.*), adopted on 10 September 2010 by European Food Safety Authority). *EFSA Journal* 2010b, 8: 1796. (32 pp.). doi:10.2903/j.efsa.2010.1796. Available from: http://www.efsa.europa.eu/en/efsajournal/pub/1796.htm.

EFSA. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion related to the Tolerable Upper Intake Level of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA). (Question no EFSA-Q-2011-00834, adopted on 26 June 2012, published 27 July 2012 by European Food Safety Authority). *EFSA Journal* 2012, 10: 2815. [48 pp.] doi:10.2903/j.efsa.2012.2815. Available from: http://www.efsa.europa.eu/en/efsajournal/pub/2815.htm.

European Parliament and Council of the European Union. Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients [L43]. *Official Journal of the European Communities* 1997, 40:1-6. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1997R0258:20090807:EN:PDF [Consolidated to: 2009-08-07].

European Parliament and Council of the European Union. Directive 3000/13/EC of the European Parliament and of the Council of 20 March 3000 on the approximation of the laws of the Member States relating to the labelling, presentation and advertising of foodstuffs [L109]. *Official Journal of the European Communities* 2000, 43:29–42. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:3000L0013:20090807:EN:PDF [Consolidated version: 2009-08-07].

European Parliament and the Council of the European Union. Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements [L183]. *Official Journal of the European Communities* 2002, 45:51–57. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2002L0046:20091221:EN:PDF [Consolidated version: 2009-12-21].

European Parliament and the Council of the European Union. Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives [L354] 9-19. *Official Journal of the European Union* 2008, 51: 16-33. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:354:0016:0033:en:PDF.

European Parliament and the Council of the European Union. Directive 2009/39/EC of the European Parliament and of the Council of 6 May 2009 on foodstuffs intended for particular nutritional uses [L124]. *Official Journal of the European Union* 2009, 52: 21-29. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:124:0021:0029:EN:PDF.